

## PATENT SPECIFICATION

(11) 1250531

1250531

## NO DRAWINGS

- (21) Application No. 102/69 (22) Filed 1 Jan. 1969  
 (23) Complete Specification filed 16 Dec. 1969  
 (45) Complete Specification published 20 Oct. 1971  
 (51) International Classification C 07 d 55/20; A 61 k 27/00  
 (52) Index at acceptance

C2C 170—189—276 1171—191—280 173—197—288  
 173—199—272 175—270—276 17X—191—278  
 183—199—283 184—188—272 200 211 213 215  
 220 221 222 225 226 227 22Y 246 247 250 251  
 252 25Y 28X 29X 29Y 305 30Y 311 313 31Y  
 320 321 32Y 332 334 338 339 342 345 34Y 351  
 354 364 36X 36Y 500 509 50Y 57X 602 610 63X  
 64X 650 661 670 671 672 680 694 701 703 709  
 717 726 737 747 790 79Y KY KZ LA LH LW  
 LY MV

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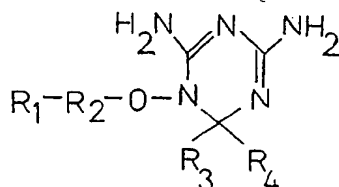
- (72) Inventors: PATRICK MAMALIS and DENNIS JAMES  
 OUTRED

(54) DI-HYDRO TRIAZINE DERIVATIVES AND PROCESSES  
 FOR THEIR MANUFACTURE

(71) We, BEECHAM GROUP LIMITED, a British Company, of Beecham House, Great West Road, Brentford, Middlesex, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to N-substituted symmetrical di-hydrotriazine derivatives and to processes for making them. Compounds within the scope of the present invention have anti-microbial activity of various kinds, including anti-malarial activity.

Accordingly the present invention provides novel N-substituted symmetrical di-hydrotriazine derivatives



where R<sub>1</sub> is an aromatic ring system, a heterocyclic group or a non aryl carbocyclic ring system of 3—8 carbon atoms, all of which rings may be substituted or unsubstituted;

R<sub>2</sub> is a substituted or unsubstituted divalent aliphatic group of 2—16 carbon atoms;

R<sub>3</sub> is hydrogen or lower alkyl of 1—4 carbons, and R<sub>4</sub> is lower alkyl of 1—4 carbons, where R<sub>3</sub> and R<sub>4</sub> may be the same or different and may be linked to form a spiro-cycloalkane or loweralkylspirocycloalkane group including the 2-carbon of the triazine ring

and salts and acyl derivatives thereof, except that R<sub>1</sub> is not an unsubstituted phenyl group when R<sub>2</sub> is unsubstituted and that R<sub>1</sub> is not 1-methyl-2-naphthyl when R<sub>2</sub> is ethylene.

Within the definition of R<sub>1</sub> we wish to include: aryl, including partially hydrogenated aryl and polycyclic aryl, cycloaliphatic, including saturated and unsaturated cycloaliphatic and heterocyclic groups.

R<sub>1</sub> may for example be phenyl, naphthyl, phenanthryl, pyrenyl, anthryl, tetrahydronaphthyl and tetrahydrophenyl; cycloalkyl, including cyclopentyl, cyclohexyl, cycloheptyl and methylcyclohexyl; cycloalkenyl, including



cyclohexenyl, heterocyclic, including pyridyl, pyrrolidinyl, piperazinyl, imidazolyl, benzimidazolyl, phthalimido, quinolyl, furyl and thienyl.

- 5 The group  $R_1$  may have a wide range of substituents: it may for example, where the nature of  $R_1$  itself is appropriate be mono- or poly-substituted by hydrocarbon groups e.g. aryl; alkyl, including methyl and ethyl; cycloalkyl of 3—8 carbon atoms including cyclohexyl, cyclopentyl and cycloheptyl; halogen, including chlorine and bromine; nitro; halogeno-lower alkyl, including mono-, di- and tri-chloro-, fluoro- or bromo- lower alkyl; lower alkoxy including methoxy, ethoxy and propyloxy; lower alkoxy carbonyl, including methoxycarbonyl, ethoxycarbonyl and propyloxycarbonyl; arylloweralkyl, including benzyl and phenylethyl; carboxy; hydroxyl; mercapto; cyano; loweralkylthio, including methylthio and ethylthio; loweralkyl sulphonyl; alkoxy-sulphonylalkyl; hydroxy-loweralkyl, including 2-hydroxyethyl; loweralkoxy alkyl; cyano-loweralkyl; sulphonamido; amino and mono- and di-loweralkylamino, including methyl- and ethyl- amino. When  $R_1$  has more than one substituent these may be the same or different. In general unless otherwise specified these groups may have 1—24 carbon atoms if the prefix "lower" is not used and 1—6 carbon atoms if the prefix "lower" is used.

- Within the definition of  $R_2$  we wish to include straight chain or branched divalent aliphatic groups both saturated and unsaturated.  $R_2$  may for example be propylene, vinylene, 3-methylpropylene,  $-(CH_2)_n-$  where  $n$  is 1—16, but is preferably a straight chain alkylene of 2—8 carbon atoms, e.g. tetramethylene.

- $R_2$  may be mono- or poly- substituted for example with hydroxy, lower alkoxy of 1—6 carbon atoms or halogen.

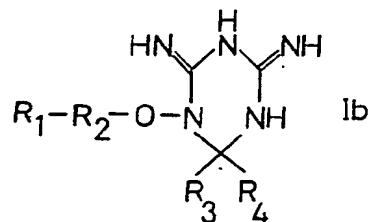
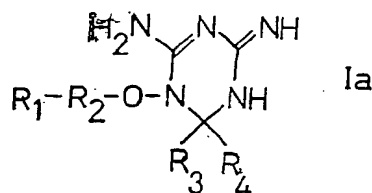
- One preferred group of compounds are those of the general formula I wherein  $R_1$  is a substituted aryl ring system (except when  $R_2$  is substituted or unsubstituted) or a substituted or unsubstituted heterocyclic group or a substituted or unsubstituted cycloalkyl group of 3 to 8 carbon atoms and  $R_2$  is a divalent aliphatic hydrocarbon radical containing 2 to 16 carbon atoms which may be straight chain or branched and mono or poly substituted by hydroxyl, methoxy, or halogen which may be the same or different.

- $R_3$  and  $R_4$  may for example be methyl, hydrogen and ethyl or may be linked to form a spirocycloalkane group including the 2-carbon atom of the triazine ring for example spirocyclohexane or 4-methylspirocyclohexane.

- Although formulae have been used herein in order to represent the compounds of the present invention, the value of the present invention does not depend upon the precise theoretical correctness of these formulae. The names and formulae used herein are not

intended to limit the invention to any specific tautomeric form or to any specific optical or geometric isomer.

Structures of the following form may for example contribute towards formula I.



The compounds of the present invention are conveniently prepared in the form of acid addition salts, since the free base tends to be somewhat unstable, and a wide range of acids may be used. If the compounds are to be applied pharmaceutically, then the acid should of course have acceptable pharmaceutical properties such as low toxicity.

Thus the compounds of the present invention may be made in the form of the monohydrohalic acid addition salts for example the hydrobromide or the hydrochloride. Other salts may be made however by simple reaction of base with acid and may be desirable in order to modify the properties of the product such as its toxicity, taste, physical form or rate of release into the body. For example the compounds may be made in the form of the picrate, saccharinate, acetate, acid maleate, acid phthalate, succinate, phosphate, *p*-nitrobenzoate, stearate, mandelate, *N*-acetyl-glycine, pantoate, cyclohexyl sulphamate, citrate, tartrate, or gluconate.

Stable salts are normally formed with a ratio one molecule of triazine to one molecule of monobasic acid (or more than one molecule of triazine in the case of polybasic acids) but the possibility of having basic groups as substituents in  $R_1$  for example means that further quantities of acid may be combined with the triazine in some cases.

The presence of the amino groups on the triazine ring of formula I creates the possibility of forming acyl derivatives by reaction with acylating agents such as acyl halides, anhydrides and acyl azides. One to four acetyl groups for example may be associated with the compound of formula I although in some cases it may be more difficult to make derivatives having higher numbers of acetyl groups.

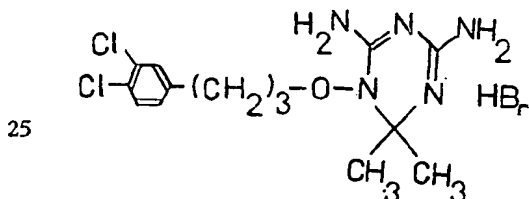
The present invention therefore includes compounds of formula I in the form of acyl derivatives (for example loweraliphatic acyl, such as acetyl derivatives or benzoyl).

- 5 In certain preferred compounds of the present invention  $R_1$  is phenyl or naphthyl substituted by one or more halogen atoms, especially chlorine. Preferably also  $R_2$  is a saturated aliphatic group containing 2—8 carbon atoms and  $R_3$  and  $R_4$  are both methyl.

- 10 Compounds within the scope of the present invention have activity against bacteria, protozoa, parasites, including the Plasmodia of malaria, fungi including dermatophytes and *Candida*, and also display coccidiostatic properties in certain cases.

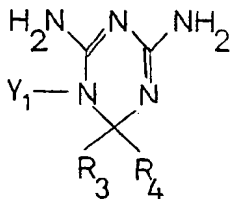
- 15 Thus activity has been observed against *Staph. aureus*, *Escherichia coli*, *Candida albicans*, *Proteus mirabilis*, *Pseudomonas pyocyanea* and *Streptococcus haemolyticus*.

- 20 For example 4,6 - diamino - 1,2 - dihydro-2,2 - dimethyl - 1 - [3 - (3,4 - dichlorophenyl)propyloxy] - 1,3,5 - triazine hydrobromide of formula



displays activity against cycloguanil-sensitive and cycloguanil-resistant strains of *Plasmodium berghei* in the mouse.

- 30 The present invention also provides a process for the preparation of the compounds of the present invention which comprises reacting a triazine



### III

- where  $Y_1$  is a reactive group with a compound  $R_2Y_2$  which is capable of reacting with  $Y_1$  so as to form the group  $R_1R_2O$ — or an intermediate group capable of conversion thereto and where necessary converting the intermediate group to  $R_1R_2O$ — and optionally where necessary forming a salt.

- 40 Preferably  $Y_1$  and  $Y_2$  are OH or derivatives of OH capable of reacting with each other to form an oxygen linkage. Thus at least one of  $Y_1$  and  $Y_2$  should contain an oxygen atom.

Conveniently  $Y_1$  is OH (see formula VI) or OM where M is a metal for example sodium, potassium or lithium and  $Y_2$  is chlorine, bromine or iodine. Other reactive derivatives of the OH group include sulphonic acid derivatives.

In a preferred process a compound  $R_1R_2Z$  where Z is chlorine or bromine is reacted with the hydroxy triazine VI in an inert solvent or diluent. Examples of suitable solvents include dimethyl sulfoxide, dimethylformamide or ethanol.

The hydroxy triazine derivative VI is usually obtained in the form of an acid addition salt (e.g. the hydrochloride) from which the free base may be liberated by one equivalent of base such as an alkali metal hydroxide (e.g. potassium hydroxide) or sodium in ethanol or methanol. The mixture may then be evaporated and reacted in a suitable solvent (e.g. dimethylformamide or dimethylsulphoxide). Preferably extra base is not added, since with two equivalents of sodium in alcohol for example a less pure product is obtained.

In a modified procedure, usually giving poorer yields, the hydrochloride of compound VI in dimethylformamide or dimethylsulphoxide is reacted with one equivalent of aqueous potassium hydroxide (using as little water as possible) and the resulting mixture reacted to give a triazine hydrohalide.

The  $Y_1$  N-substituted triazine III may be made from an appropriately substituted diguanide as outlined hereinafter or by any other convenient method.

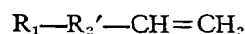
The side-chain  $R_1R_2O$  may be attached in a variety of ways and may be attached in one reaction or in a multi stage process. Normally the minimum number of stages is employed to achieve optimum yields, for convenience and other factors.

Thus well-known ether-forming synthetic methods may be used to link the side-chain to the triazine with the O atom previously in place on either the side-chain or the triazine. Typical examples are

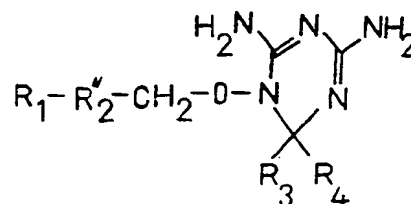
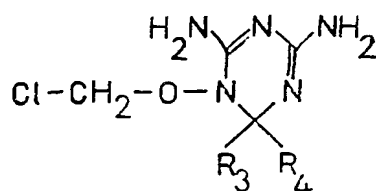
1. the reaction of a halide with a hydroxyl compound with or without added base as previously described.

2. the reaction of a reactive ester such as a sulphonate with a hydroxyl compound.

In another process a compound of general formula



may be reacted with the hydroxy triazine VI where  $R_2'$  is  $R_2$  in formula I minus two carbon atoms. Alternatively compounds within the scope of the present invention may be made by reacting the hydroxy triazine VI with formaldehyde in the presence of hydrochloric acid to form a compound of formula



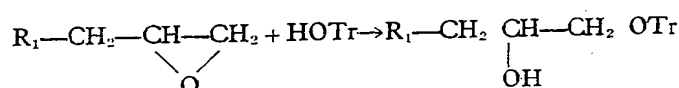
and reacting this with a compound of formula



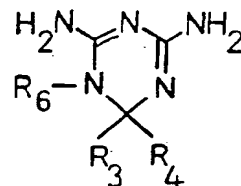
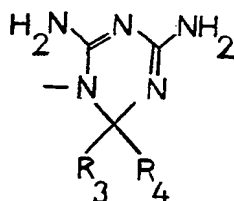
- 5 where  $\text{R}_2''$  is  $\text{R}_2$  in formula I minus one carbon atom, to form compounds of general formula

Alternatively certain hydroxy substituted compounds within the scope of the present invention may be made by reacting an appropriately substituted ethylene oxide with the hydroxy triazine VI as illustrated by the reaction scheme

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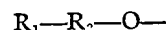
- 15 where Tr is used to represent



35

V

and converting  $\text{R}_6$  where necessary into



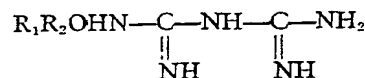
- 20 Reactions of the types illustrated above may clearly be performed using either the hydroxy-triazine VI as a starting material or a triazine with a partial side-chain already in place although in many cases such a partial side-chain triazine may be made from the hydroxy-triazine originally.

- 25 A further aspect of the present invention provides a process for the preparation of the compounds of the present invention which comprises reacting a substituted diguanide of formula

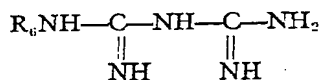
and optionally where necessary forming a salt.

Preferably the acid is a strong acid such as hydrochloric or formic acid and at least one molecular equivalent is used. The reaction may in some cases be carried out without any further solvents or diluents but usually an inert solvent such as a lower aliphatic alcohol (e.g. methanol) is preferred.

When  $\text{R}_6$  is  $\text{R}_1-\text{R}_2-\text{O}-$  the substituted diguanide II becomes



IVa



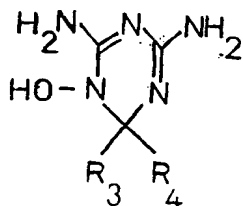
IV

- 30 where  $\text{R}_6$  is  $\text{R}_1-\text{R}_2-\text{O}-$  or a group capable of conversion thereto with a carbonyl compound  $\text{R}_3 \cdot \text{CO} \cdot \text{R}_4$  in the presence of an acid catalyst to form a substituted triazine of formula V

and accordingly the present invention also provides compounds of this kind for use as intermediates in the process of the present invention. Compound IVa may be made for example by reacting a bromide of general formula  $\text{R}_1\text{R}_2\text{Br}$  with benzohydroxamic acid and treating this with acid to form an oxamine of formula  $\text{R}_1\text{R}_2\text{ONH}_2$  which is subsequently reacted with dicyandiamide.

55

- Alternatively the group  $R_4$  may be chosen so as to be convertible into the group  $R_1R_2O$ . For example  $R_4$  may be a group which is capable of undergoing catalytic hydrogenolysis. Thus  $R_4N$ -substituted triazine may be formed from an appropriately substituted diguanide and then hydrogenolysed to produce the hydroxy triazine VI



VI

- $R_4$  may for example be substituted or unsubstituted benzyloxy or substituted or unsubstituted naphthylmethyloxy and the hydrogenolysis may be carried out with hydrogen in the presence of a palladium catalyst.
- The hydroxytriazine VI may then be reacted in a variety of ways well understood by those skilled in the art and as indicated previously to produce the desired substituted triazine of formula I. A preferred method is to react VI with a compound  $R_1R_2Y_3$  where  $Y_3$  is a reactive group displaceable by a nucleophilic group.
- It will be further understood by those skilled in the art that the side-chain  $R_2-R_2-O$  may be built up or attached in stages either before or after the substituted diguanide IV is converted to the substituted triazine V.
- The final product may be obtained in the form of an acid addition salt as a consequence of the reaction without the necessity of a separate step of salt formation but if necessary the additional step of reacting the free base with an acid to form a salt may be performed. Salts can be converted back to the free base by treatment with alkali (e.g. KOH) and then converted to other salts as required by conventional means.
- Acyl derivatives may also be made by reacting the base with acyl derivatives as previously described.
- The present invention also provides pharmaceutical compositions for use against malaria comprising as active ingredient a compound according to the present invention together with a pharmaceutically acceptable carrier.
- Thus the active compounds of this invention may be employed for the treatment and prevention of malaria in man. Therefore, one aspect of the present invention is a method of treatment or prevention of malaria in man which comprises administering one of the active compounds to the person infected or at risk. The compound may be administered

orally, parenterally, or by suppository, though the oral route is preferred.

As stated above the compound of this invention may be administered orally, parenterally or by suppository. The water solubility of the hydrochloride of the compound and most other salts is low and the hydrochloride is non-hygroscopic. If solutions are required it will be necessary to add solubilising agents to the water, choose non-aqueous solvents, find a more soluble salt or prepare very dilute solutions.

Oral formulations are preferred and with the above proviso in connection with solutions, typical oral formulations will include tablets, pills, capsules, sachets, granules, powders, chewing gum, suspensions, emulsions and solutions: particularly preferred oral formulations are tablets and capsules. Where appropriate and where necessary the formulations may include diluents, binding agents, dispersing agents, surface-active agents, lubricating agents, coating materials, flavouring agents, colouring agents, solvents, thickening agents, suspending agents, sweeteners or any other pharmaceutically acceptable additives, for example gelatin, lactose, starch, talc, magnesium stearate, hydrogenated oils, polyglycols and syrups. Where the formulations are tablets or capsules and the like they will represent pre-measured unit doses but in the case of granules, powders, suspensions and the like the formulations may be presented as pre-measured unit doses or in multi-dose containers from which the appropriate unit dose may be withdrawn.

The injectable form may be an aqueous or non-aqueous solution, suspension, or emulsion in a pharmaceutically acceptable liquid (e.g. sterile pyrogen-free water or parenterally acceptable oils) or mixture of liquids which may contain bacteriostatic agents, antioxidants or other preservatives, buffers, (preferably in the physiological pH range of 6.5-7.0), solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi-dose forms such as a bottle from which the appropriate dose may be withdrawn, or as a solid form or concentrate which can be used to quickly prepare an injectable formulation. All formulations for injection are preferably rendered sterile. Suppositories containing the compound will also contain suitable carriers (e.g. cocoa butter or polyglycols).

In addition to standard pharmaceutical additives there may be included within formulations of the compound other therapeutic agents, particularly including other anti-malarials (e.g. sulphonamides).

Examples of the invention will now be described:

## EXAMPLE 1

4,6 - diamino - 1,2 - dihydro - 2,2 - dimethyl - 1 - [3 - (3,4 - dichlorophenyl)propyloxy] - 1,3,5 - triazine hydrobromide

- 5 Benzhydroxamic acid (137 g., 1.0 mol.) and I.M.S. (a mixture of ethanol with a few % methanol) (1.5 litres) are placed in a flask equipped with a stirrer, dropping funnel and condenser, and stirred until solution is complete. A solution of NaOH (40 g., 1.0 mol.) in water (100 ml.) is added with vigorous stirring. The sodium salt of benzhydroxamic acid may precipitate at this stage.

- 10 Benzyl bromide (170 g., 120 ml.) is added dropwise over 45 minutes, the mixture gradually becomes clear, leaving only a small amount of inorganic material undissolved. The reaction is preferably left at room temperature for 3 days, refluxing for 1—2 hours will give slightly lower yields.

- 15 The solvent is removed under reduced pressure and the oily residue is dissolved in ethyl acetate and washed several times with water. The solvent extract is dried with magnesium sulphate, filtered and evaporated to dryness under vacuum.

- 20 The solid residue is triturated with ether and collected to give the required benzyl benzhydroxamate ( $C_6H_5CONHOCH_2C_6H_5$ ) m.p. 100—102°C.

- 25 The benzyl benzhydroxamate (170 g.) is dissolved in methanol (500 ml.) and concentrated hydrochloric acid (165 ml.) is added. The mixture is refluxed for 3 hours, filtered hot, and allowed to crystallise. The solid collected by filtration is washed well with ether, until no smell of methyl benzoate remains. Yield of amino-oxymethylbenzene hydrochloride:

- 30 First crop 120 g. m.p. 227—230° (sealed tube). Concentration of the mother liquors and treatment with ether gives a further crop, 20 g. m.p. 220—225° (sealed tube).

- 35 Total yield=140 g. (ca. 90%).  
45 Amino oxymethyl benzene hydrochloride (97.5 g.) and dicyandiamide (51.4 g.) are dissolved in I.M.S. (300 ml.) with stirring and warming. The mixture is then refluxed for 3 hours, filtered if necessary, and evaporated under reduced pressure. The oily residue is dissolved in water and treated with strong aqueous NaOH (ca. 6N) with stirring. The diguanide base which separates, solidifies on cooling and is collected, washed with water and dried.

- 50 The yield of benzyloxy diguanide base is 95—100 g. m.p. 98—100° (80%).

- 55 Benzyloxydiguanide base (52 g.) is dissolved in I.M.S. (200 ml.) and concentrated hydrochloric acid (43 ml.) is added, followed by acetone (200 ml.). Preferably, the reaction is left at room temperature for 3 days but a 2—3 hour reflux period will give slightly lower yields. Some triazine usually separates, and

may be collected by filtration, washed with water and dried. 65

The mother liquors are evaporated to dryness and the residue triturated with acetone, to give a white solid. The solid is collected washed with water and dried. 70

Total yield of 4,6 - diamino - 1,2 - dihydro - 2,2 - dimethyl - 1 - benzyloxy - 1,3,5 - triazine hydrochloride 61 g. m.p. 204—206° (80%).

41 parts of 4,6 - diamino - 1,2 - dihydro - 2,2 - dimethyl - 1 - benzyloxy - 1,3,5 - triazine hydrochloride dissolved in 320 parts of ethanol and 220 parts of water was shaken with hydrogen and 0.25 to 1.0 parts of 10% palladised charcoal catalyst, that is a catalyst composed of acid washed active charcoal (90 parts) on which has been adsorbed ten parts by weight of metallic palladium in a finely divided form, at room temperature and atmospheric pressure until the uptake of hydrogen ceased. The catalyst was filtered off and the filtrate evaporated to dryness to give 4,6 - diamino - 1,2 - dihydro - 2,2 - dimethyl - 1 - hydroxy - 1,3,5 - triazine hydrochloride (24.5 parts), m.p. 234—235°C (decomp.). 75

Crystallisation from ethanol gave needles, m.p. 237°C (decomp.). The production described in this Example may be effected using a platinum catalyst as described below: 80

11 Parts of 4,6 - diamino - 1,2 - dihydro - 2,2 - dimethyl - 1 - benzyloxy - 1,3,5 - triazine hydrochloride dissolved in 200 parts methanol and 100 parts water were shaken with hydrogen and platinum oxide at room temperature and atmospheric pressure until a 10% excess over the theoretically calculated hydrogen uptake was observed. Hydrogenation was stopped, the catalyst removed and the clear filtrate evaporated to dryness at reduced pressure. The solid residue was triturated with acetone and the 4,6 - diamino - 1,2 - dihydro - 2,2 - dimethyl - 1 - hydroxy - 1,3,5 - triazine hydrochloride collected in theoretical yield, m.p. 234° (decomp.). 85

4,6 - Diamino - 1,2 - dihydro - 2,2 - dimethyl - 1 - hydroxy - 1,3,5 - triazine hydrochloride (1.93 g.) dissolved in methanol (25 ml.) was treated with a solution of KOH (0.7 g.) in methanol (15 ml.). The mixture was refluxed for 20 minutes and the solvent removed at reduced pressure. The residue was suspended in dimethylformamide, and treated with 3 - (3,4 - dichlorophenyl)propyl bromide (3.0 g.). The mixture was stirred at room temperature for one hour, and then gently warmed until a clear solution was obtained. The solution was filtered, and evaporated to dryness, the residue was triturated with acetone, and the white solid collected, (3.2 g.) m.p. 190—193. This material was washed with water and recrystallised from ethanol to give the pure triazine (1.7 g.) m.p. 203°C, 4,6 - diamino - 1,2 - dihydro - 2,2 - dimethyl - 1 - [3 - (3,4 - dichlorophenyl)propyloxy] - 1,3,5 - triazine hydrobromide. 90

## EXAMPLE 2

4,6 - Diamino - 1,2 - dihydro - 2,2 - dimethyl-  
1 - (6 - (cyclohexyl)hexyloxy) - 1,3,5-  
triazine hydrobromide  
5 6 - (Cyclohexyl) - hexyl bromide was pre-  
pared by the treatment of 6 - (cyclohexyl)-  
hexan - 1 - ol with a mixture of HBr (48%)  
and H<sub>2</sub>SO<sub>4</sub> (28:3 parts by volume). The  
mixture was refluxed for 6 hours, diluted with  
10 water, and extracted with ether. The extract  
was washed with water, dilute NaHCO<sub>3</sub>  
solution and water, dried over MgSO<sub>4</sub>. After  
filtration and removal of the solvent, the oily  
residue was distilled at 1 mm. pressure. The  
15 fraction boiling at 112—114°C was the  
required bromide  $n_D^{25}$  1.4840.

The above bromide (7.5 g.) was reacted with  
the base derived from 4,6 - diamino - 1,2-  
dihydro - 2,2 - dimethyl - 1 - hydroxy - 1,3,5-  
triazine hydrochloride (5.8 g.) and KOH 20  
(2.1 g.) as described above. The reaction was  
heated with stirring at 90—100° for 6 hours.  
After working up in the previously described  
manner, the required triazine was obtained  
(5.0 g.) m.p. 203°C, 4,6 - diamino - 1,2 - di- 25  
hydro - 2,2 - dimethyl - 1 - (6 - (cyclohexyl)-  
hexyloxy) - 1,3,5 - triazine hydrobromide.

## EXAMPLES 3—41

The following compounds were made by a  
process closely similar to that described in 30  
Example 2. Symbols have the meanings  
ascribed to them in formula I.

Ex. No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	Salt	m.p. °C.
3	3,4—Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	(CH <sub>2</sub> ) <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HBr	216
4	3,4—Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	(CH <sub>2</sub> ) <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HBr	203
5	4—ClC <sub>6</sub> H <sub>4</sub>	(CH <sub>2</sub> ) <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HBr	210
6	C <sub>6</sub> H <sub>5</sub>	CHCl·CHCl·CH <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HBr	187
7	4—NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	(CH <sub>2</sub> ) <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HCl	206
8	N-Pyrrolidyl	CH(CH <sub>3</sub> )CH <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HCl	183—185
9	N'-Methyl-N-piperazinyl	CH(CH <sub>3</sub> )CH <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HCl	153—155
10	4—Cl C <sub>6</sub> H <sub>4</sub>	(CH <sub>2</sub> ) <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HBr	190—192
11	Cyclohexyl	(CH <sub>2</sub> ) <sub>6</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HBr	203
12	Cyclohexyl	(CH <sub>2</sub> ) <sub>6</sub>	—(CH <sub>2</sub> ) <sub>5</sub> —		HBr	225—226
13	3,4—Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	(CH <sub>2</sub> ) <sub>4</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HBr	225
14	2—CH <sub>3</sub> —5—NO <sub>2</sub> — imidazolyl	(CH <sub>2</sub> ) <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HCl	193
15	4-Pyridyl	(CH <sub>2</sub> ) <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HBr	200
16	Cyclohexyl	(CH <sub>2</sub> ) <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HBr	186
17	Cyclohexyl	(CH <sub>2</sub> ) <sub>3</sub>	—(CH <sub>2</sub> ) <sub>5</sub> —		HBr	242
18	2,6—Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	CH(CH <sub>3</sub> )	CH <sub>3</sub>	CH <sub>3</sub>	HBr	216
19	2,4—Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	CH(CH <sub>3</sub> )	CH <sub>3</sub>	CH <sub>3</sub>	HBr	201
20	3,4—Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	CH(CH <sub>3</sub> )	CH <sub>3</sub>	CH <sub>3</sub>	HBr	214—216
21	3,4—Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	CH(C <sub>2</sub> H <sub>5</sub> )	CH <sub>3</sub>	CH <sub>3</sub>	HBr	209—210
22	2,4—Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	CH(C <sub>2</sub> H <sub>5</sub> )	CH <sub>3</sub>	CH <sub>3</sub>	HBr	201—202
23	2,6—Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	CH(C <sub>2</sub> H <sub>5</sub> )	CH <sub>3</sub>	CH <sub>3</sub>	HBr	185—187

Ex. No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	Salt	m.p. °C.
24	2,4—Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	CH(C <sub>2</sub> H <sub>5</sub> )	H	C <sub>2</sub> H <sub>5</sub>	HBr	188—190
25	2,6—Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	CH(C <sub>2</sub> H <sub>5</sub> )	H	C <sub>2</sub> H <sub>5</sub>	HBr	185—187
26	3,4—Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	CH(CH <sub>3</sub> )	H	C <sub>2</sub> H <sub>5</sub>	HBr	213—215
27	2,4—Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	CH(CH <sub>3</sub> )	H	CH <sub>3</sub>	HBr	225—227
28	3,4—Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	CH(CH <sub>3</sub> )	H	CH <sub>3</sub>	HBr	225—227
29	2,4—Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	CH(CH <sub>3</sub> )	H	C <sub>2</sub> H <sub>5</sub>	HBr	188—190
30	2,6—Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	CH(CH <sub>3</sub> )	H	C <sub>2</sub> H <sub>5</sub>	HBr	217—219
31	2-Benzimidazolyl	(CH <sub>2</sub> ) <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	2.HBr 1.H <sub>2</sub> O	246—247
32	3,5—(CH <sub>3</sub> ) <sub>2</sub> —Phenyl	(CH <sub>2</sub> ) <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HBr	233—235
33	4—NH <sub>2</sub> —Phenyl	(CH <sub>2</sub> ) <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HBr	215
34	N-Phthalimido	(CH <sub>2</sub> ) <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HBr	201—203
35	N-1,2,3,4-Tetrahydro- iso quinoline	(CH <sub>2</sub> ) <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	2.HBr	ca 100
36	cycloHexyl	(CH <sub>2</sub> ) <sub>4</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HBr	196—198
37	3—CF <sub>3</sub> Phenyl	(CH <sub>2</sub> ) <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HBr	185
38	1-Naphthyl	(CH <sub>2</sub> ) <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HBr	220—222
39	3,4—Cl <sub>2</sub> Phenyl	CH=CH—CH <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HBr	209
40	1—Cl—2-naphthyl	(CH <sub>2</sub> ) <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HBr	194—196
41	2,4—Cl <sub>2</sub> —phenyl	CH=CH—CH <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HBr	190—191

## EXAMPLE 42

4,6 - Diamino - 1,2 - dihydro - 2,2 - dimethyl-  
1 - [3 - (3,4 - dichlorophenylpropyloxy)] -  
1,3,5 - triazine hydrochloride

- 5 Benzhydroxamic acid (13.7 g.) was dissolved  
in methanol (100 ml.) and a solution of NaOH  
(4.0 g.) in 10 ml. of water was added. 3 - (3,4-  
10 dichlorophenyl)propyloxy bromide (26.8 g.)  
was added dropwise with stirring. When the  
addition was complete the mixture was  
refluxed for 3 hours, the solvent evaporated  
and the residue dissolved in water and  
15 extracted with ethyl acetate. The solvent  
extract was washed with water, dried and  
evaporated to yield a pale yellow viscous oil  
which slowly crystallised. The required benz-  
hydroxamate was obtained by trituration with  
20 ether and filtration to give a white solid which  
could be crystallised from ethanol to yield the  
pure compound.

3 - (3,4 - dichlorophenyl)propyl benz-  
hydroxamate (16.2 g.) was refluxed with a  
mixture of methanol (120 ml.) and concen-  
trated hydrochloric acid (40 ml.) for 2 hours. 25  
The reaction mixture was filtered and evapor-  
ated under reduced pressure and the residue  
was triturated with ether, filtered and washed  
well with ether to yield 3 - (3,4 - dichloro-  
phenyl)propyloxyamine hydrochloride. This 30  
compound (12.8 g.) and dicyandiamide (6.3 g.)  
were dissolved in ethanol (100 ml.) and  
refluxed for 3 hours. The reaction mixture was  
evaporated to dryness under reduced pressure  
and the residual gum was dissolved in water 35  
and basified with 4N NaOH solution: an oil  
separated which slowly solidified. The solid  
was collected by filtration, washed well with  
water and dried in a vacuum desiccator. The  
3 - (3,4 - dichlorophenyl)propyloxy diguanide 40  
thus obtained was a cream coloured solid



which darkened on prolonged exposure to light. The crude material could be recrystallised from ethyl acetate/petrol to yield the pure compound.

- 5 15.2 g. of the pure compound was dissolved in methanol (50 ml.) and 8.6 ml. of concentrated hydrochloric acid was added followed by 50 ml. of acetone and the mixture refluxed for 3 hours. The reaction mixture was filtered and evaporated to dryness under reduced pressure, the residue was titrated with acetone and filtered. The white solid obtained was washed well with water, dried and recrystallised from ethanol to yield 4,6 - diamino - 1,2-dihydro - 2,2 - dimethyl - 1 - [3 - (3,4 - dichlorophenyl)propyloxy] - 1,3,5 - triazine hydrochloride, m.p. 235—237°C (decomp.).

#### EXAMPLE 43

- 20 Acyl derivatives of 4,6 - diamino - 1,2-dihydro - 2,2 - dimethyl - 1 - [3 - (3,4-dichlorophenyl)propyloxy] - 1,3,5-triazine

##### a) Diacetyl derivative

- 25 The triazine of the title (1.0 g.) and redistilled acetic anhydride (10 ml.) were heated on a steam bath for 5 minutes. Excess acetic anhydride was removed by evaporation and the residue dissolved in ethyl acetate. 40—60°C petrol was added, followed by crystallisation under cool conditions to give a yield of 0.5 g., m.p. 125°C.

The melting point remained constant on recrystallisation (ethyl acetate/petrol 40—60°C).

##### b) Tetraacetyl derivative

- 35 The triazine (1.0 g.), triethylamine (5 ml.) and redistilled acetic anhydride (10 ml.) were stirred at room temperature for 70 hours. The reaction mixture was poured onto ice and stirred for 1 hour followed by extraction with ethyl acetate. Extracts were washed with water, dried over  $MgSO_4$ , decolourised with charcoal and solvent removed by evaporation. The residue was recrystallised from ethyl acetate/petrol 40—60°C.

- 45 Yield=0.4 g., m.p. 84°C.

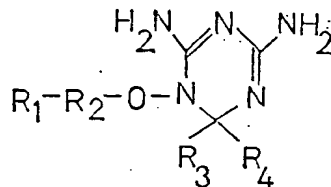
On recrystallisation (ethyl acetate/petrol 40—60°C) m.p. = 85°C.

##### c) Di-benzamide

- 50 The triazine (2.0 g.) and benzoic anhydride (10 g.) were heated in a steam bath for 30 minutes. The reaction mixture was cooled and triturated with ether to give a white solid, m.p. 128—130°C.

#### WHAT WE CLAIM IS:—

1. N-substituted symmetrical dihydro triazine derivatives of general formula



where  $R_1$  is an aromatic ring system, a heterocyclic group or a non aryl carbocyclic ring system of 3—8 carbon atoms, all of which rings may be substituted or unsubstituted;

$R_2$  is a substituted or unsubstituted divalent aliphatic group of 2—16 carbon atoms;

$R_3$  is hydrogen or lower alkyl of 1—4 carbon atoms and

$R_4$  is lower alkyl of 1—4 carbon atoms, where  $R_3$  and  $R_4$  may be the same or different or may be linked to form a spirocycloalkane or lower-alkylspirocycloalkane group including the 2-carbon of the triazine ring and salts and acyl derivatives thereof, except that  $R_1$  is not an unsubstituted phenyl group when  $R_2$  is unsubstituted and that  $R_1$  is not 1 - methyl - 2 - naphthyl when  $R_2$  is ethylene.

2. A compound as claimed in claim 1 in which  $R_1$  is phenyl or naphthyl both of which may be substituted or unsubstituted.

3. A compound as claimed in claim 2 in which  $R_1$  is substituted by one or more halogen atoms.

4. A compound as claimed in claim 3 in which the halogen is chlorine.

5. A compound as claimed in any one of the preceding claims in which  $R_2$  is saturated aliphatic.

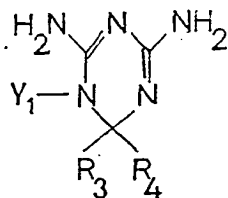
6. A compound as claimed in claim 5 in which  $R_2$  is straight chain alkylene of 2—8 carbon atoms.

7. A compound as claimed in any one of the preceding claims in which  $R_3$  and  $R_4$  are both methyl.

8. 4,6 - diamino - 1,2 - dihydro - 2,2 - dimethyl - 1 - [3 - (3,4 - dichlorophenyl)propyloxy] - 1,3,5 - triazine hydrobromide.

9. A compound as claimed in claim 1 in which  $R_1$  is a substituted aryl ring system (except when  $R_2$  is substituted in which case  $R_1$  may be substituted or unsubstituted) or a substituted or unsubstituted heterocyclic group or a substituted or unsubstituted cycloalkyl group of 3—8 carbon atoms and  $R_2$  is a divalent aliphatic hydrocarbon radical containing 2—16 carbon atoms which may be straight chain or branched and mono or poly substituted by hydroxyl, methoxy or halogen which may be the same or different.

10. A process for the preparation of a compound as claimed in any one of the preceding claims which comprises reacting a triazine



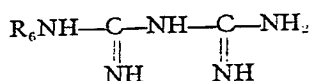
5 where  $Y_1$  is a reactive group with a compound  $R_5Y_2$  which is capable of reacting with  $Y_1$  so as to form the group  $R_1-R_2-O-$  or an intermediate group capable of conversion thereto and where  
10 necessary converting the intermediate group to  $R_1-R_2-O-$  and optionally where necessary forming a salt.

11. A process as claimed in claim 10 in which  $Y_1$  and  $Y_2$  are OH or reactive derivatives thereof at least one of which contains an oxygen atom.

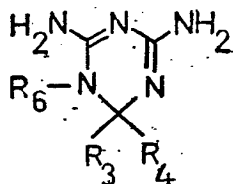
12. A process as claimed in claim 11 in which  $Y_1$  is OH and  $Y_2$  is chlorine, bromine or iodine.

13. A process as claimed in any one of claims 10—12 in which  $R_5$  is  $R_1-R_2-$ .

14. A process for the preparation of a compound as claimed in any one of claims 1—9 which comprises reacting a substituted  
25 diguanide of formula



where  $R_6$  is  $R_1-R_2-O-$  or a group capable of conversion thereto, with a carbonyl compound  $R_3R_4CO$  in the presence of an acid  
30 catalyst to form a compound

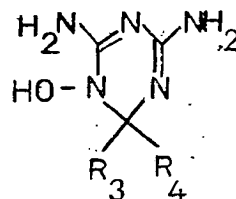


and where necessary converting  $R_6$  into  $R_1-R_2-O-$  and optionally where necessary forming a salt.

15. A process as claimed in claim 14 in which  $R_6$  is  $R_1-R_2-O-$ .

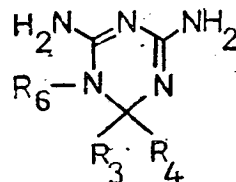
16. A process as claimed in claim 14 or claim 15 in which the acid catalyst is a strong acid and in which the reaction is performed in  
40 the presence of an inert solvent or diluent.

17. A process as claimed in claim 14 in which  $R_6$  is capable of hydrogenolysis to OH which comprises forming a compound



and subjecting this to hydrogenolysis to convert  $R_6$  to OH.

18. A process as claimed in claim 17 in which  $R_6$  is a group capable of conversion to OH and which comprises converting  $R_6$  to OH  
50 to form a compound of formula



and then reacting this with a compound  $R_1R_2Y_3$  where  $Y_3$  is a reactive group displaceable by a nucleophilic group to form the compound in which  $R_1-R_2-O$  replaces  $R_6$ .

19. A process as claimed in claim 17 in which  $R_6$  is substituted or unsubstituted benzyl-  
55 oxy or naphthylmethyloxy.

20. A process as claimed in claim 18 or claim 19 in which the hydrogenolysis is performed by treatment with hydrogen in the presence of a palladium catalyst.

21. A process as claimed in any one of claims 10—20 which comprises the additional step of reacting the product with an acylating reagent to form an acyl derivative.

22. A process as claimed in claim 21 in which an acylating reagent is used.

23. A substituted triazine when made by a process as claimed in any one of claims 10—20, 21 or 22.

24. A pharmaceutical composition for use in the treatment or prevention of malaria which comprises a compound as claimed in any one of claims 1—9 or 23 in combination  
75 with a pharmaceutically acceptable carrier.

25. A composition as claimed in claim 24 which also contains another anti-malarial.

26. A composition as claimed in claim 25 in which the other anti-malarial is a sulphonamide.

27. A compound as claimed in claim 1 and as described in any one of examples 1—43.

28. A process for the preparation of a compound as claimed in claim 1 and as described in any one of examples 1—43.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1971.  
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from  
which copies may be obtained.

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